

PREGNENOLONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

G. NORMAN MYERS

Regional Medical Research Centre, Royal Bath Hospital, Harrogate

Since Hench, Kendall, Slocumb, and Polley (1949) described their results from the administration of cortisone (17-hydroxy-11-dehydrocorticosterone) and of the anterior pituitary adrenocorticotrophic hormone in the treatment of rheumatoid arthritis, there has been much speculation regarding the possible use of other substances which might produce similar effects. The search for such substances has been confined primarily to two main groups:

- (a) those, like adrenaline, which are known to stimulate the production of the anterior pituitary corticotrophic hormone,
- (b) those which may be precursors of more active steroid hormones.

From the chemical standpoint Δ -5-pregnenolone has been suggested as a precursor and has attracted the attention of a number of workers.

Davison and others (1950) treated thirty arthritis patients with pregnenolone acetate, fourteen of whom were suffering from rheumatoid arthritis. Solutions in oil, as well as aqueous suspensions, were administered by the intramuscular route. Daily injections, up to 200 and 300 mg. respectively, were given over a period of 3 to 8 weeks. They reported results which appear to be definitely favourable. Pain and stiffness in joints was diminished, muscle strength was increased, and fatigue was less evident. A feeling of "well-being" was established, usually within a few days. Reduction in joint swelling was slow, and reduction in the erythrocyte sedimentation rate, if any, did not run parallel with the clinical improvement, but followed it. No toxic effects were observed; the menstrual cycle and sexual potency were unaffected. None of the subjects under test experienced euphoria, but one patient suffered from insomnia while receiving the maximum dosage. When the injections were discontinued, the arthritic symptoms returned within a few days. No beneficial effects were observed in cases of rheumatoid arthritis with psoriasis, severe gout, or disseminated lupus.

Ishmael and others (1949) employed pregnenolone in doses up to a maximum of 100 mg. daily, as well as in combination with high-dosage androgen and oestrogen therapy. They reported that when pregnenolone was administered alone, about 50 per cent. of the patients with rheumatoid arthritis responded favourably. One patient, however, developed mental depression and a feeling of weakness.

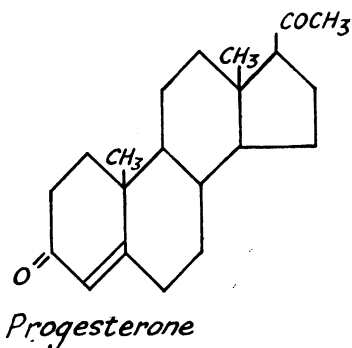
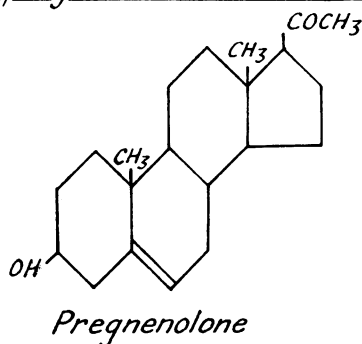
Freeman and others (1950) also describe improvement following the administration of pregnenolone. Thirty patients suffering from rheumatoid arthritis were given pregnenolone, or pregnenolone acetate, orally over a period of six weeks, the daily dose being 500 mg. Of these patients 50 per cent. showed a decided improvement, and another 30 per cent. showed some degree of amelioration of symptoms. The remaining 20 per cent. showed no change. Of sixteen subjects in whom treatment was discontinued, improvement was maintained for an average period of six weeks. No toxic effects were observed.

Guest and others (1950) administered pregnenolone by the intramuscular route daily, or two or three times weekly, to nineteen patients. Seventeen cases of rheumatoid arthritis showed no improvement; one patient with rheumatoid spondylitis improved objectively and subjectively, and another showed minor subjective improvement at the end of one week's treatment, which was followed by a relapse in spite of continued therapy. Stock and McClure (1950), who treated ten cases for 2 weeks with a daily dose of 200 mg., reported an objective improvement in three cases.

Copeman and others (1950) studied the effect of pregnenolone on eight cases of polyarthritis of the rheumatoid type. A uniform dose of 300 mg. per day was employed for nine days. No significant change was recorded other than an unexplained rise in pregnanediol excretion on the 7th day. The erythrocyte sedimentation rate rose during treatment.

It has been suggested that pregnenolone may be an intermediate substance in the synthesis and metabolism of certain steroid compounds present in the body. It has been isolated from the testes of the hog by Ruzicka and Prelog (1943), and is thought by some to be a precursor of testosterone as well as of progesterone.

Δ -5-pregnen-3(β)-ol-20-one



So far it has not been isolated from human sources (Tyler, 1949). It can be synthesized from cholesterol and stigmasterol by oxidation of the C₂₀ side chain. By suitable oxidation, pregnenolone can also be converted into dehydroisoandrosterone, deoxycorticosterone, or progesterone. These oxidative conversions can be performed *in vitro*, but no evidence has so far been produced to show that they can take place in the body. Hoagland (1944) claimed that the daily administration

of 25 to 27 mg. pregnenolone to factory workers augmented their physical output by about 18 per cent. This dosage was well tolerated and no secondary effects were observed. Gasche and Schuler (1946), using rats, report an absence of oestrogenic effects with doses up to 200 mg./kg. A progesterone-like action on castrated rabbits was observed by Miescher and Gasche (1943).

Methods

All the subjects selected for this investigation were in-patients showing definite signs of rheumatoid arthritis in more than one joint. The duration of the disease varied in the different subjects and the severity of the condition was assessed in accordance with the therapeutic criteria and related aids in rheumatoid arthritis recommended by the American Rheumatic Association (Steinbrocker and others, 1949).

For the purpose of the present investigation it was thought desirable to study the long-term effects of pregnenolone, in addition to some short-term effects, and it was decided to vary the individual dosage and the period of administration over wide limits. The dosage employed varied between 10 and 300 mg. per day, and the periods of administration ranged from 5 to 44 days. In most cases the pregnenolone was given in solution as an intra-muscular injection into the upper and outer quadrant of the buttock. In a few cases the injections gave rise to pain; this was most evident where a large dosage was employed. Whenever this occurred, the intramuscular dose was reduced and the balance given in the form of sublingual tablets. In two cases the sublingual route was used exclusively during the whole of the trial period.

Estimations of the erythrocyte sedimentation rate (E.S.R.) by the Spa Hospitals Method, plasma viscosity, packed-cell volume, erythrocyte and leucocyte counts, eosinophil count, and haemoglobin were made during the two days preceding the administration of pregnenolone, during the period of administration, and for at least one week after the drug had been discontinued.

All the subjects received routine physiotherapy throughout the whole period. In order to avoid psychological effects, they were informed that they were not receiving cortisone or ACTH, but that the substance under test was part of a clinical trial to ascertain any blood changes which might follow its use. Throughout the trial it was obvious that they did not expect anything to happen, at least, anything which they would be able to observe. All other drugs were withheld during the period covered by the trial.

Assessment of Clinical Effects

Observations were confined to those effects which might be expected to give as clear-cut an answer to the problem as possible. They were based on both subjective and objective observations, in addition to results obtained in the clinical laboratory. The range of joint-movement, power of hand grip, etc., were recorded.

Five male and five female in-patients were selected. In three subjects the disease appeared to follow direct injury to the body, though not necessarily to the joints affected. A brief outline of each case is given.

After examination they were graded according to the recommendations of Steinbrocker and others (1949); as may be seen in Table I, the ages varied from 15 to 50 years, and the duration of symptoms from 8 months to 10 years. The gradings were unaltered by the use of pregnenolone.

Table II shows the dosage of pregnenolone employed and the frequency and duration of administration in each case. Total dosage varied from 0.09 g. given over a period of 9 days to 12.3 g. in 41 days.

TABLE I
CLASSIFICATION OF CASES
(*American Rheumatic Association Code*)

Patients				Before Pregnenolone		After Pregnenolone	
Case No.	Sex	Age (years)	Duration of symptoms (years)	Stage (progression)	Functional capacity	Functional capacity	Response (grade)
1	F	15	2½	2	2	2	3
2	F	18	3	3	3	3	4
3	M	33	12	3	4	4	4
4	M	38	2½	1	2	2	3
5	M	25	8 mths	2	2	2	3
6	F	25	8 mths	1	2	1	3
7	M	37	1	2	2	2	3
8	F	24	7	3	2	2	3
9	F	23	5	2	2	2	3
10	M	50	9	3	3	3	4

TABLE II
DOSAGE, E.S.R., AND PLASMA VISCOSITY

Case No.	Sex	Dosage					Sedimentation rate (per cent.)		Plasma Viscosity	
		Amount (mg.)	Route	Frequency	Duration (days)	Total Administered (g.)	Before Pregnenolone	After Pregnenolone	Before Pregnenolone	After Pregnenolone
1	F	200	oral	daily	40	8	16-8	13-7	20·3	20·0
2	F	100	intramuscular	daily	5	0·5	42-44	42-39	21·6	20·9
3	M	100	intramuscular	daily alternate days	9 22	2	52-43	51-41	25·2	22·4
4	M	300	intramuscular	daily	23	6·9	36-37	46-44	22·0	21·8
5	M	300 100 200 300 100 200	intramuscular intramuscular oral intramuscular oral intramuscular	daily daily daily daily	7 13 8 13	2·1 3·9 2·4 3·9	48-43	50-44	22·4	21·4 22·6
6	F	300 300	intramuscular oral	daily daily	22½ 18½	6·6½ 5·4½	46-43	50-44 47-42	24·2	23·2 23·4
7	M	300	oral	daily	36	10·8	16-16	20-23	18·2	19·2
8	F	30	intramuscular	daily	8	0·24	32-21	32-26	21·4	21·3
9	F	10	intramuscular	daily	9	0·09	25-17	27-16	19·8	19·1
10	M	10 60 150 300	intramuscular intramuscular intramuscular oral	daily daily alternate days daily	14 7 12 21	0·14 0·42 1·80 6·30	21-21 24-22 40-40	21-22 24-22 45-43	19·2 22·2 20·0	22·2 19·0 21·5

Examination of the erythrocyte sedimentation rates and plasma viscosity shows little or no change as a result of pregnenolone administration except in Cases 4, 7, and 10. Case 4 showed an increased sedimentation rate without any alteration in plasma viscosity. A similar increase was seen in Case 7, here the viscosity was also slightly increased. Case 10 is particularly interesting; here there was no change

until the 21st day, when the E.S.R. showed a remarkable increase. The plasma viscosity followed a similar but less spectacular course.

No changes in E.S.R. or plasma viscosity were recorded in seven out of ten cases; the other three cases all showed an increase in sedimentation rate.

During this period the clinical results showed a remarkable agreement with the results set out above. No patients showed any change in their condition except Cases 4, 7, and 10. All three complained of increased pain and stiffness in the affected joints five to seven days before the E.S.R. increase was recorded. In Cases 4 and 7 this was not nearly so marked as in Case 10.

The increased pain was not accompanied by any joint swelling, but in Case 10 the pain was so severe as to keep him awake at night unless given special analgesic medication. He had a high threshold for pain, and rarely complained even when it was very severe, but movement of the joints at this stage produced wincing. There was redness and swelling around the joints.

The leucocyte and eosinophil counts before and after pregnenolone only are set out in Table III. The intermediate counts, which showed nothing decisive, have been omitted. No conclusive results can be drawn from these figures. The high eosinophil counts seen in Cases 1, 3, 6, and 10 bore no relationship to the severity of activity of the disease. The counts, before the administration of pregnenolone, of Cases 1 and 2 might be taken as an example. Case 2 had a lower eosinophil count than Case 1, and yet the arthritic condition was much worse. On the other hand, Case 10, having the highest eosinophil count, had the disease in a more actively acute stage and, in this respect, was worse than any of the others.

TABLE III
BLOOD COUNT

Case No.	Before Pregnenolone		After Pregnenolone		Total Dosage	
	Eosinophils (per c.mm.)	Leucocytes (thousands)	Eosinophils (per c.mm.)	Leucocytes (thousands)	days	g.
1	155	8.2	45	7.4	40	8
2	50	8.3	80	8.2	5	0.5
3	200	7.2	220	7.5	30	2
4	110	11.4	175	7.8	23	6.9
5	90	6.2	—	6.9	41	12.3
6	200	11.0	—	8.4	40	12.0
7	80	5.7	145	7.0	36	10.8
8	130	6.0	100	6.5	8	0.24
9	140	5.0	145	8.0	9	0.09
10	530	6.4	190	8.2	54	8.66

The leucocyte counts showed no constant change in response to pregnenolone. In five cases they were substantially the same before and after pregnenolone; two cases showed a marked reduction, and three showed a slight increase.

The results of the erythrocyte counts, haemoglobin and packed-cell volume determinations are set out in Table IV which shows no significant alteration in any of these totals after pregnenolone therapy.

TABLE IV
BLOOD EXAMINATION

Case No.	Stage	Red-Blood Cells (millions)	Haemoglobin (per cent.)	Colour Index	Packed-Cell Volume (%)
1	Before	4.7	78	0.83	36
	After	4.4	80	0.87	37
2	Before	5.4	90	0.84	44
	After	5.0	82	0.82	40
3	Before	4.7	66	0.70	36
	After	4.6	64		35
4	Before	6.1	90	0.74	43
	After	6.0	84		41
5	Before	4.9	78	0.82	39
	After	5.1	80		42
6	Before	5.2	82	0.79	40
	After	5.0	80		39
7	Before	5.2	100	0.96	42
	After	5.2	100	0.96	45
8	Before	4.5	74	0.83	35
	After		78		38
9	Before	4.6	83	0.9	37
	After	4.1	76	0.92	35
10	Before	4.4	85	0.97	42
	After	4.9	90	0.92	41

Unfortunately the eosinophil response to adrenaline was assessed in only four cases (Table V). One showed a marked reduction in circulating eosinophil cells, and another a slight response, but the other two showed no change.

TABLE V
EOSINOPHIL RESPONSE TO ADRENALINE

Case No.	Sex	Age (years)	Duration of Symptoms (years)	Eosinophils per c.mm.	
				Before adrenaline (10 a.m.)	After adrenaline (2 p.m.)
3	M	33	12	220	175
4	M	38	2½	175	164
6	F	25	8 mths	200	200
8	F	24	7	130	45

Case Reports

Case 1. Female, aged 15 years.—Two and a half years ago she experienced pain in both legs, which was quickly followed by swelling of the ankles. Four months later the finger joints became affected and the wrists were soon involved. The condition is said to have dated from the onset of menstruation. There is no family history of rheumatoid arthritis.

The hands and feet are cold and moist and subject to chilblains. The onset of the disease was afebrile, acute, and polyarticular.

Examination.—The interphalangeal joints of both hands show fusiform swelling and the wrists are swollen. The feet are painful and swollen at the first metatarso-phalangeal joints. The ankles are also slightly swollen. Nothing abnormal was found in the respiratory, cardiovascular, urinary, or nervous systems. Digestion is good. Blood pressure 110/74 mm. Hg.

X-Ray Examination.—The carpal bones show osteoporosis. There is a definite narrowing of the joint spaces in both wrists, which is most marked in the os magnum and semilunar bone of the left wrist and the radiocarpal in the right wrist. There is general osteoporosis of the bones in the feet. The ankle joints appear to be normal.

Laboratory Findings.—Serum colloidal gold reaction—positive (5); B.M.R. +6 per cent.; creatinine in urine 1.25 mg. per 100 ml.

Therapy.—200 mg. pregnenolone were given orally for 40 days. Clinical examination during the period of administration showed no definite evidence of improvement in her condition. She continued to have pain in both hands, especially in the early morning when she awakened. The pain in the ankles varied from day to day, but was always worse when she walked. The pain in the right shoulder, however, became much easier. Her general health improved and she gained in weight. Three weeks after the pregnenolone had been stopped, she believed that she was walking a little better and with less pain. X ray revealed no change in the condition of her joints.

Case 2. Female, aged 18 years.—The disease commenced two and a half years ago with pain and swelling of the right foot. Within a few months the left foot and left knee were affected. A few months before the onset of the disease she fell on some rocks and cut the dorsum of her right foot. The lesion healed very slowly and signs of rheumatoid arthritis were evident shortly afterwards. The onset was insidious and afebrile, and affected one joint only. There is no family history of rheumatic disease.

Examination.—Nothing abnormal was found in the respiratory, nervous, or urinary systems. The blood pressure was 105/55 mm. Hg. The second pulmonary sound was accentuated and a soft diastolic murmur was present along the left sternal border. The heart was normal in size. The appetite is poor. Her weight was 6 st. 5 lb., being normally 7 st. 1 lb. There was limitation of the movements of both ankles, with pain on movement. All movements of the hip joints were minimal. Abduction of the feet was only about three to four inches and even this was accomplished with great pain. She found walking difficult, not only because of the pain in her hip joints, but because of an added pain in the groin and lumbar region. There was marked wasting of the muscles of both thighs and legs. The left knee was swollen and painful when moved.

X-Ray Examination.—Both ankles and feet show advanced rheumatoid changes in addition to marked calcaneal spurs on both heels. Both knees show generalized bone rarefaction with stencilling of the outlines such as is seen in the early phase of rheumatoid arthritis. The hip joints show early signs of arthritis. The spinal curves are deficient, the disk spaces appear normal.

Laboratory Findings.—Serum colloidal gold reaction—negative; B.M.R. +22 per cent.; creatinine in blood 0.5 mg. per 100 ml.

Therapy.—100 mg. pregnenolone were given intramuscularly for 5 days. No change in her clinical condition was observed during the period of administration. Three weeks later she had less pain in her hips and was walking a little better. The improvement was not very marked, nor was it sustained.

Case 3. Male, aged 33 years.—Twelve years ago he experienced a feeling of very marked fatigue after a long motor journey. A few days later, after swimming, he had a sudden pain in the joints of both great toes. He continued to work for three months in spite of a painful limp, before being seen by an orthopaedic surgeon who diagnosed pes planus. Later he was sent to hospital as a case of rheumatoid arthritis and treated with protein shock and gold therapy. The results were disappointing. For some years the pain and swelling of the joints continued and, in time, the metacarpo-phalangeal joints of both thumbs became involved. Slowly the condition became quiescent until two years ago when the right shoulder became involved. During the past six months he has developed

stiffness in both mandibular joints and in the lumbo-sacral region. The left knee has become swollen and painful and he has lost about 1 st. in weight during the past three months. The onset of the arthritis was acute, afebrile, and polyarticular. His family history is particularly interesting; two brothers died in childhood with rheumatic fever, and one sister had rheumatic fever as a child.

Examination.—There is swelling of the carpal and metacarpo-phalangeal joints of each thumb, both joints are ankylosed. The ankles are slightly swollen with tenderness over the heads of the metatarsals. The spine shows limited movement throughout. His normal body weight was 10 st., but he now weighs 7 st. 12½ lb. The chest has a poor expansion (1¼ in.), and there is dyspnoea on exertion. X-ray examination shows a fair degree of lung fibrosis, especially on the right side, but there is no evidence of any active lesion. The digestive, nervous, urinary, and cardiovascular systems are normal. The blood pressure, 106/78 mm. Hg, is low. There is sweating of the hands and feet, but no evidence of any marked peripheral vascular disturbance.

X-Ray Examination.—There are signs of bilateral sacro-iliac arthritis and osteoporosis of the lumbar vertebrae and slight scoliosis of the upper dorsal spine, with narrowing of the disk space at the level of the 4th and 5th cervical vertebrae. The right shoulder and the metatarso-phalangeal joints of both feet show advanced arthritic changes.

Laboratory Findings.—Serum colloidal gold reaction—positive (5).

Therapy.—100 mg. pregnenolone were given intramuscularly for 9 days, when it was reduced to alternate days because of a slight rise in temperature to 99° F. which lasted 2 days. The injections were continued on alternate days for 22 days. No alteration in his clinical condition was observed. His weight remained constant at 8 st.

Case 4. Male, aged 38 years.—In February, 1948, he noticed swelling of the fingers which was soon followed by joint stiffness and pain. In April, 1950, his knees became affected and a month later his left shoulder and elbows became very stiff. Although the stiffness diminished, he has had intermittent pain in the left arm since then. No other members of his family have had rheumatism.

Examination.—The proximal interphalangeal and metacarpo-phalangeal joints of both hands are swollen. The wrists are stiff and painful. There is pain and tenderness over the metatarsal heads of both feet. His present weight is 11 st., 2 st. having been lost during the past 18 months. There were no signs of any marked peripheral vascular disorders.

Laboratory Findings.—Serum colloidal gold reaction—negative; B.M.R. +5 per cent.

Therapy.—300 mg. pregnenolone were given intramuscularly for 23 days. Seven days after the injections were started, he became distinctly cheerful and announced that the pain and stiffness had completely disappeared from his hands and that he had less pain in the feet. On the 21st day he stated that he had no pain in any of his joints, that the joints did not feel so stiff, and that they moved more freely. Clinical examination showed no alteration in the range of the joint movements, but an almost complete absence of joint pain. When discharged from hospital on the 34th day, he said that he was still free from joint pain and stiffness and was pleased at the progress he had made.

Case 5. Male, aged 25 years.—Acute onset in January, 1950, one week after an accident to his left hand. The left index finger became swollen and pain commenced in the proximal interphalangeal and metacarpo-phalangeal joints and in the left wrist. One week later the left knee became affected and on the following day the right ankle became painful. Within a few days the right knee became involved and after a further three weeks the right shoulder and both wrists were swollen and painful. Three weeks ago slight swelling and redness around the interphalangeal joint of the left great toe and the left temporo-mandibular joint became evident. The onset of the disease was febrile, acute, and monarticular. His recent past history reveals treatment of psychoneurosis with insulin shock therapy. There is nothing of interest in his family history.

Examination.—He is a big, broad-shouldered type, and somewhat adipose. There is a fusiform swelling of the left 3rd metacarpo-phalangeal joint. The 1st metatarso-phalangeal joints

Soon afterwards the knees, shoulders, hands, elbows, and wrists became swollen and painful. The family history shows nothing of importance except that one sister had an attack of "rheumatism" which quickly disappeared. There is no evidence of peripheral vascular disturbances in the hands or feet.

Examination.—There are fusiform swellings of the 1st, 2nd, and 3rd metacarpo-phalangeal joints of both hands. Both wrists are swollen and painful, while both ankles have a limited range of movement. He has lost weight since the onset of the arthritis and now weighs 9 st. 4 oz. (normal weight 11 st.). No abnormality of the respiratory, cardiovascular, digestive, urinary, or nervous systems was found.

X-Ray Examination.—The left knee shows definite generalized bone rarefaction. Similar changes, but less advanced, are present in the right knee. The distal interphalangeal joints of both hands show early marginal hypertrophic changes and all interphalangeal joint spaces are narrowed. Areas of rarefaction are present in the heads of the 2nd, 3rd, and 4th metacarpal bones of the right hand.

Laboratory Findings.—Serum colloidal gold reaction—positive (2); glucose tolerance test normal; plasma uric acid 4 mg. per 100 ml.

Therapy.—300 mg. pregnenolone were given for 36 days by sublingual route. During the first 17 days the patient experienced considerable pain, worse than before pregnenolone administration, in both feet. On the 18th day the pain abated, but he was conscious of stiffness in the feet and thighs which eased after about 20 minutes exercise. There was no change in body weight. From this time onwards his general health improved, his joint pains lessened and he began to think less of himself and more about his surroundings and the other patients. By the 36th day he had gained 10 lb. in body weight, his joint pains were negligible, and he was able to get about more freely than before pregnenolone administration. Next day he was discharged on a daily maintenance dose of 50 mg. Examination five weeks later showed that he had continued to improve at home and was able to work a full day from 7.30 a.m. to 5.30 p.m. as a foreman plater, without any difficulty. He had some slight pain on pressure over the 4th metacarpo-phalangeal joint of the right hand in addition to tenderness on the plantar surface of his feet. This patient showed a marked clinical improvement during the 36 days he was given pregnenolone, in spite of the increase in plasma viscosity and E.S.R. over the same period.

Case 8. Female, aged 24 years.—Had tonsillitis seven years ago. Four weeks later she experienced pain and stiffness of the fingers, which was most marked in the mornings. The pain spread to the feet, which became swollen. She has had three courses of gold without effect. During the past year the elbow joints and mandibular joints have become involved. In consequence she finds it difficult to feed herself or brush her teeth. Onset of the disease was afebrile, insidious, and polyarticular. There is no family history of rheumatoid arthritis. No signs of peripheral vascular disturbances have been observed beyond frequent attacks of chilblains.

Examination.—Movements of both hands and wrists are limited. There are fusiform swellings of the metacarpo-phalangeal and proximal interphalangeal joints of both hands and wrists. The metatarsal joints of both feet and the right ankle are painful and slightly swollen. There is a complaint of stiffness in the hip joints and the lumbar spine. Her present weight is 8 st. 12 lb. (normal 10 st. 2 lb.). No abnormality was detected in the respiratory, cardiovascular, nervous, digestive, or urinary systems. The blood pressure is low (98/60 mm. Hg).

X-Ray Examination.—Both hands and wrists show widespread joint destruction. The first metatarso-phalangeal joints of both feet are affected, the scaphoid joint and the left shoulders. The left elbow shows evidence of some articular erosion of the sigmoid fossa. The knees, ankles, and spine appear normal. The left shoulder shows osteoporosis and evidence of acromioclavicular arthritis.

Laboratory Findings.—Serum colloidal gold reaction—negative.

Therapy.—30 mg. pregnenolone were given for eight days intramuscularly. Examination at the end of the period showed no clinical change in her condition. The plasma viscosity and erythrocyte sedimentation rate were substantially unaltered. However,

of both feet are painful and tender to pressure. The left temporo-mandibular joint and the right sterno-costal joints are tender.

X-Ray Examination.—The internal femoral condyles of both knees show in their lateral views, rarefaction of bone beneath the articular surfaces. There is generalized osteoporosis, particularly in the tarsus of the right foot.

Laboratory Findings.—Plasma uric acid 3.6 mg. per 100 ml.; B.M.R. +10 per cent.

Therapy.—He was started on a daily intramuscular injection of 300 mg. pregnenolone. On the 7th day he complained of pain in both buttocks at the site of the injections. The daily injection was then reduced to 100 mg. and the balance of 200 mg. was given in tablet form by the sublingual route. This method of administration was continued for the next 13 days, when the intramuscular route was again resorted to. At the end of a further 8 days it was again found necessary, because of pain, to reduce the daily intramuscular injection to 100 mg. and to give the balance of 200 mg. in sublingual tablets. Objectively there was no material alteration in his clinical condition during the first 8 days on pregnenolone. He still complained of pain and stiffness in both hands and knees, although his general manner was more cheerful. On the 10th day he stated that there was a great reduction in the pain in the affected joints, particularly in the feet and knee joints. At this time, however, the hands began to show swelling over the length of the metacarpal bones of both hands, especially the left. By the 15th day the feet and knees showed further improvement while the left hand showed signs of inflammation of the 3rd metacarpo-phalangeal joint which was hot, tender, swollen, and inflamed. On the 21st day his general health had improved appreciably. There was less pain in the hands, but more in the feet. On the 36th day the 3rd and 4th metacarpo-phalangeal joints were still very painful, but less swollen, and there was less pain in the knees and feet than at any time since the investigation was started. He had gained 2 st. in weight since his admission to hospital 2 months earlier. His left hand was still swollen and painful on the 50th day, when he discharged himself.

Case 6. Female, aged 25 years.—In January, 1950, she complained of pain, fatigue, and swelling of the right ankle. The left foot and ankle were soon involved and later the knees, shoulders, and wrists. More recently the hands became affected. For three months the disease progressed slowly, but then became more acute. By June she was unable to follow her employment. The onset was afebrile, insidious, and polyarticular. The family history shows no evidence of rheumatoid arthritis.

Examination.—There is a malar flush. The patient is slightly obese, but there is evidence of recent loss of body weight. Her present weight is 10 st. 11 lb. (previously 13 st.). The hands show slight fusiform swellings of the proximal interphalangeal joints. The metatarso-phalangeal joints of both feet are tender and painful, as well as the ankles. The respiratory, digestive, urinary, and nervous systems appear normal. The cardiovascular system revealed nothing of importance. The hands and feet were cold and sweaty.

X-Ray Examination.—There is slight osteoporosis of the left knee joint in addition to the tarsal and other bones of both feet. The plantar arches are dropped.

Laboratory Findings.—Serum colloidal gold reaction—positive (3); B.M.R. +1 per cent.

Therapy.—300 mg. pregnenolone were given intramuscularly for 22 days, when pain, tenderness, and signs of inflammation developed at the sites of the injections. The injections were discontinued, and she was given 300 mg. daily by the sublingual route for a further 18 days. There was no change in her condition until the 14th day, when she stated that the pains in her feet were much less, but that the ankles were worse. Clinically there appeared to be great pain on movement of the ankles. The range of ankle and knee movements had not altered. On the 40th day, when the pregnenolone administration was stopped, there was no objective change in her condition, although she believed that she had made a general improvement.

Case 7. Male, aged 38 years.—Onset afebrile a year ago with pain in his right ankle.

one year later she had improved to such an extent that she had returned to her work as a typist and could work a full day without any ill effect.

Case 9. Female, aged 24 years.—Rheumatoid arthritis of five years duration. It began with stiffness of the proximal interphalangeal joint of the middle finger of the right hand. The other fingers were soon involved as well as those of the left hand. Six months later the feet were affected and the condition remained static for about two years. At this time she became pregnant and the stiffness and much of the swelling disappeared. Three months after delivery, her condition was as bad as ever. Since then the disease has spread to the wrists, shoulders, and knees, and her general health has deteriorated with loss of weight. She had a course of gold therapy in 1946 followed by a temporary improvement. A second course in 1948 caused a mild dermatitis. There is no family history of rheumatism. The onset of the disease was afebrile, insidious, and polyarticular. No peripheral vascular disturbances have been observed.

Examination.—There are fusiform swellings of the proximal interphalangeal joints and metacarpo-phalangeal joints of both hands and wrists. There are also fusiform swellings of the metatarso-phalangeal joints of both feet. Her present weight is 7 st. 12 lb. (normal 9 st.). Nothing abnormal was found in the respiratory, cardiovascular, nervous, digestive, or urinary systems.

X-Ray Examination.—The hands and wrists show marked narrowing of the articular spaces. There is also narrowing of the spaces in the proximal interphalangeal joints of the left middle finger and the ring finger of the right hand. The other finger joints are affected in a lesser degree. Osteoporosis is generalized, but slight. The appearances of the feet are similar to the hands. There is some bone absorption of the superior surface of the left scaphoid. The knees and ankles are normal.

Laboratory Findings.—Serum colloidal gold reaction—positive (1); plasma uric acid 3.7 mg. per 100 ml.

Therapy.—10 mg. pregnenolone were given intramuscularly for 9 days. There was no change in her clinical condition in response to the injections, nor was there any change in the plasma viscosity, erythrocyte sedimentation rate, or general blood picture.

Case 10. Male, aged 50 years.—In 1941 this patient was on active service with H.M. Forces in Iceland, where he was subject to extremes of climate such as blizzards, gales, and adverse weather conditions. His general health was excellent until he was involved in a motor accident, when a car in which he was travelling fell about 40 ft. over a precipice. He suffered no immediate serious results of the accident. For about 18 months he experienced pain and tenderness in the hands and feet without any swelling. Then the proximal phalangeal joints of both hands became swollen and painful. The onset of the condition was afebrile, insidious, and polyarticular. He has never experienced any peripheral vascular disturbances in the hands, fingers, feet, or toes, and no reaction to a change of locality has been observed. From 1942, when the first signs of rheumatoid arthritis became evident, his condition became slowly, but progressively, worse. Since 1948 the disease has become more acute and painful. There is no history of rheumatism in his family as far back as his maternal and paternal grandparents. In June, 1949, he was admitted to hospital.

Examination.—He is a thin type weighing 9 st. 4 lb. (weight in 1942 10 st. 12 lb.). There are marked rheumatoid deformities with ulnar deviation in both hands. The cardiovascular, nervous, and digestive systems are normal. There was no history of any infections or disturbances of the genito-urinary system. There was marked difficulty in walking on account of tenderness of his feet and muscular pain in the calves and thighs, especially after exercise. Both arms showed wasting of hand, forearm, and arm muscles in addition to a limitation of movements. They were easily fatigued. Movement of the mandibular joints produced pain in the right side.

X-Ray Examination.—The bones of both hands show generalized osteoporosis. There are marked deformities with erosion of bone. The condition of the metacarpo-phalangeal joints and interphalangeal joints could not be determined because of the extensive destruction. The right foot showed arthritis in the first metatarso-phalangeal joint with centres of rarefaction in the region of the second metatarso-phalangeal joint.

Laboratory Findings.—Serum colloidal gold reaction—positive (3); B.M.R. —15 per cent.

Therapy.—This patient was started on 10 mg. pregnenolone intramuscularly for 14 days. As no changes were recorded in his clinical condition or laboratory tests, the daily dose was increased to 60 mg. during the next 7 days—again without result.

Because of the tenderness which had developed at the site of the injections, it was decided to stop all injections for 14 days and then to increase the amount injected to 150 mg. per injection.

During the 14-day rest period, the erythrocyte sedimentation rate rose from 24-22 per cent. to 40-40 per cent. while the plasma viscosity increased from 20·0 to 21·5. Such a marked change was unexpected as well as difficult to explain. These changes were accompanied by an increase in joint pains which became so severe as to interfere with normal sleep.

In spite of this retrogression in his condition, it was decided to continue the administration of pregnenolone without further delay. This was done for 12 days, at the end of which time his condition was re-assessed. The erythrocyte sedimentation rate had risen further from 40-40 per cent. to 45-43 per cent. while the plasma viscosity had increased from 20·0 to 21·5. At this stage it was decided to abandon the intramuscular injections and to give, instead, 300 mg. pregnenolone sublingually for 21 days. This dose was well tolerated. At the end of the period there was no doubt that his arthritis had become distinctly worse. Whilst he was still in good spirits, there was not the slightest doubt that he was worried about his condition. The pain was much more intense, and he confessed that he could only bear it by taking tab. Codeine Co. Both knees were very swollen, tender, and painful. The fingers of both hands were contracted and were extremely painful to touch or to move. The ulnar deviation was marked in spite of the use of splints.

Discussion

This investigation shows that of ten patients treated with pregnenolone, only one (Case 7) showed any marked improvement. In this patient the joint pains became worse during the first 17 days; on the 18th day the pain suddenly abated and the joints remained stiff. By the 36th day the joint pains were negligible, and the patient had gained 10 lb. in body weight. In spite of this diminution in joint pain, the erythrocyte sedimentation rate and plasma viscosity showed increased values over the same period. The patient was able to walk more easily than before, but the entire improvement appeared to be due to the diminution in joint pain.

Case 4 also showed some improvement. Pain in the affected joints was reduced after 7 days' treatment; the patient developed a more cheerful outlook and his hand grip was stronger. No alteration in the range of joint movement was recorded during the trial.

A very doubtful improvement was recorded in Cases 1, 2, and 5. Case 1 showed some improvement in her general condition and gained $4\frac{1}{2}$ lb. in body weight. No clinical changes in her arthritic condition were recorded during the 40 days of pregnenolone administration, but she began to walk slightly better and with less pain three weeks after the administration was terminated. This improvement was maintained for two weeks. No alteration in erythrocyte sedimentation rate, plasma viscosity, or x-ray findings were recorded. The sequence of events in Case 2 was similar. No clinical changes were recorded while she was taking pregnenolone. Three weeks later she experienced a diminution in the pain in her hip joints and began to walk more easily. No changes were recorded in the erythrocyte sedimentation rate, plasma viscosity, or x-ray findings. Case 5 improved in

general condition and gained 2 st. in body weight while taking pregnenolone. His outlook became more cheerful after the first 7 days and, in this respect, he resembled Case 4. On the 10th day the pain in his feet and knees showed a marked diminution, but the metacarpo-phalangeal joints of both hands became swollen, inflamed, and painful. The hands became steadily worse during the next five days while the pain in the feet and knees diminished to negligible proportions. On the 21st day the condition was reversed, for the feet and knees became acutely painful, while the pain and inflammation in the hands began to subside rapidly. No explanation can be offered for this interesting observation. By the 50th day, 9 days after pregnenolone administration had ceased, all the affected joints were much less painful and swollen, and more comfortable, and the patient stated that he could use his joints a little more freely. No changes in erythrocyte sedimentation rate or plasma viscosity were recorded. The *x*-ray findings were substantially the same.

No changes were recorded in Cases 3, 6, 8, and 9. Case 6 showed no alteration until the 14th day, when her feet became less painful, while her ankles became worse. On the 40th day she believed that she had slightly improved, but the findings did not support this view.

Case 10 showed a marked deterioration during the period of pregnenolone administration. His arthritis became very acute, causing great pain and disability. Joint swelling became marked and joint tenderness increased to an almost unbearable point, while the erythrocyte sedimentation rate and plasma viscosity showed a pronounced increase.

In the only two cases who showed changes which might be regarded as an improvement in their joint condition, this appeared to be due to a diminution in joint pain and not to any constitutional changes in the body as a whole. In no case was there any immediate increase in joint movement or any marked improvement in laboratory findings such as the erythrocyte sedimentation rate, plasma viscosity, packed-cell volume, lymphocyte counts, or haemoglobin.

Three patients showed a substantial increase in body weight during the period of the trial, and two of these exhibited a more cheerful psychological outlook.

None of the female patients experienced any change in the pattern of the menstrual cycle during the period of pregnenolone administration.

As most of the changes seen in these patients were of a subjective type, it is difficult to ascribe any of the results to the administration of pregnenolone. Any, or all, of the changes may have been caused by the normal spontaneous variations frequently seen in untreated cases of rheumatoid arthritis. A larger-scale investigation might yield a more decisive result.

Summary

Ten patients, five male and five female, suffering from rheumatoid arthritis were given pregnenolone over periods varying from 5 to 54 days. The daily dose ranged from 19 to 300 mg. pregnenolone, and both intramuscular and sublingual routes were employed.

One patient showed a definite improvement in functional joint condition, another showed a moderate improvement, and three showed a very doubtful improvement. In four cases no improvement was recorded. One patient showed an acute deterioration of function, during which phase, the erythrocyte sedimentation rate and plasma viscosity were raised.

The two cases showing improvement experienced a diminution in joint pain and the improvement may be ascribed to this cause.

Three patients showed an increase in body weight, and two developed a more cheerful psychological outlook. These improvements were not accompanied by any increase in joint movement or any marked change in the erythrocyte sedimentation rate or plasma viscosity.

The pregnenolone was supplied by Messrs. Ciba, Ltd. I am indebted to Dr. G. Lorri-man for his assistance.

REFERENCES

- Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Gottlieb, B., Glyn, J. H. H., Henly, A. A., and Kellie, A. E. (1950). *Brit. med. J.*, **2**, 849.
 Davison, R., Koets, P., Snow, W. G., and Gabrielson, L. G. (1950). *Arch. intern. Med.*, **85**, 365.
 Freeman, H., Pincus, G., Johnson, C. W., Bachrach, S., McCabe, G. E., and MacGilpin, H. (1950). *J. Amer. med. Ass.*, **142**, 1124.
 Guest, C. M., Kammerer, W. H., Cecil, R. L., and Berson, S. A. (1950). *Ibid.*, **143**, 338.
 Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949). *Proc. Mayo Clin.*, **24**, 181.
 —, —, —, — (1950). *Arch. intern. Med.*, **85**, 545.
 Hoagland, H. (1944). *Science*, **100**, 63.
 Ishmael, W. K., Hellbaum, A., Kuhn, J. F., and Duffy, M. (1949). *J. Okla. med. Ass.*, **42**, 434.
 Ruzicka, L., and Prelog, V. (1943). *Helv. Chim. Acta*, **26**, 975.
 Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.
 Stock, J. P. P., and McClure, E. C. (1950). *Lancet*, **2**, 125.
 Tyler, E. T. (1949). *J. Amer. med. Ass.*, **139**, 560.

Pregnénolone dans le Traitement de l'Arthrite Rhumatismale

RÉSUMÉ

Dix malades, 5 hommes et 5 femmes, atteints d'arthrite rhumatismale, furent traités par la pregnénolone pendant des périodes de 5 à 54 jours. Ils recevaient, par la voie intramusculaire ou sous-linguale, de 19 à 300 mg. de pregnénolone par jour.

L'amélioration, portant sur la fonction articulaire, fut nette chez un malade, modérée chez un autre et très douteuse chez trois autres. Dans quatre cas on ne constata aucune amélioration. Chez un malade il eut une détérioration aiguë de la fonction, accompagnée de l'élévation de la sédimentation globulaire et de la viscosité plasmatique.

On peut attribuer l'amélioration dans les deux cas favorables à la diminution de la douleur articulaire.

Trois malades ont pris du poids et deux malades ont adopté une meilleure attitude mentale. Cette amélioration n'a pas porté sur l'amplitude du mouvement articulaire, sur la sédimentation globulaire ni sur la viscosité du plasma.

Pregnenolona en el Tratamiento de la Artritis Reumatoide

RESUMEN

Diez enfermos, 5 hombres y 5 mujeres, fueron tratados con pregnenolona durante períodos de 5 a 54 días. La dosis diaria, por vía intramuscular o perlingual, fué de 19 a 300 mg.

La función articular mejoró marcadamente en un enfermo, moderadamente en otro y dudosamente en tres. En cuatro casos no se vió mejoría alguna. En un enfermo hubo deterioración aguda de la función, con elevación de la sedimentación de los eritrocitos y de la viscosidad del plasma.

En los dos casos favorables se puede atribuir la mejoría a la disminución del dolor articular.

Tres enfermos ganaron peso y dos enfermos adoptaron una actitud más optimista. Durante esta mejoría la sedimentación eritrocitaria, la viscosidad del plasma y el movimiento articular no cambiaron.